The Role of Substance P in Simultaneously Mediating Oral Pain and Inflammation

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Substance P is the oldest peptide neurotransmitter being first discovered in 1931 by von Euler and Gaddum.[1] These investigators originally isolated substance P from extracts of horse intestine and found that it was a potent vasodilator and also caused contractions of the rabbit jejunum. Substance P was given its unusual name because it was the active *substance* in a certain chromatographic *p*reparation. As recently as 1970 substance P was purified to homogeneity and the structure determined to consist of the following sequence of eleven amino acids H-Arg-Pro-Lys-Pro-Glu-Glu-Phe-Phe-Gly-Leu-Met-NH_2.[2-3]

The first suggestions that substance P might be related to pain was made in 1953 after the demonstration that substance P was at least ten times more concentrated in the dorsal or sensory region of the spinal cord than in the ventral or motor region.[4] These authors proposed that substance P was the neurotransmitter carrying impulses to the brain within purely sensory nerves called primary afferent neurons (see figure 1). This essay will evaluate evidence suggesting that substance P is the neurotransmitter of primary afferent neurons and as such mediates dental pain following release from nerve terminals in the brain stem and also vasodilation and inflammation following release in the dental pulp.

The high concentrations of substance P within the dorsal horn of the spinal cord have recently been confirmed with fluorescent immunohistochemical studies. These reports have shown a high density of substance P fluorescent nerve terminals in the substantia gelatinosa of the dorsal horn.[5] In addition if the sensory nerve bundles coming into the dorsal horn were cut or ligated between the ganglion cell bodies and the spinal cord, the fluorescent or radioimmunoassable[7] substance P disappeared from the dorsal horn while substance P fluorescence accumulated in the nerve bundle on the ganglion side of the ligature. This indicates that substance P is synthesized in the ganglion nerve cell bodies and transported to the nerve terminals via the somatofugal axonal transport system.

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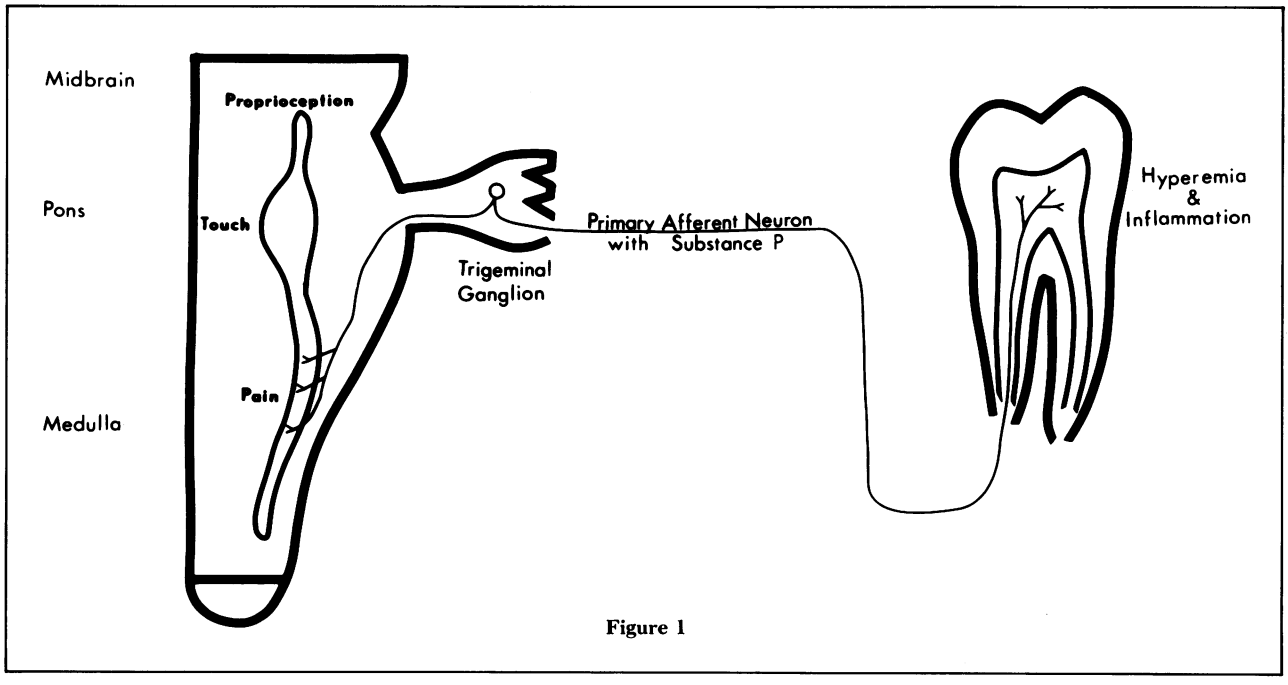

Figure 1

All of the primary afferent neurons entering the spinal cord carry sensory information such as pain, hot and cold sensations, touch, deep pressure and proprioception. However, substance P is localized within only a small population of these neurons. Thus substance P fluorescence is seen within only 20% of the ganglion cell bodies and more specifically within small myelinated Aδ fibers and small unmyelinated C fibers.[8] These smaller neurons are known to carry the sensations of pain and temperature and therefore confirm the early hypotheses of a relation between substance P and pain.

When substance P is microinjected by iontophoresis into the spinal cord, substance P excites those neurons which are excited by noxious stimulation of the skin.[9] Neurons which are activated in the spinal cord by light touch to the skin are not activated by the direct application of substance P to the spinal cord. Thus, electrophysiological data confirm the specificity of the relationship between substance P and pain.

More recent studies have focused on the importance of substance P within the trigeminal neuron system and its relationship to dental pain. Immunohistochemical[10] and radioimmunoassay[11] studies have shown fluorescense in trigeminal ganglion cells, nerve terminals in the brain stem and nerve terminals within the dental pulp. The substance P fibers in tooth pulp were found to be around blood vessels and associated with odontoblasts.[12]

The dental pulp substance P fluorescence was shown to be specific for nerves because of its disappearance fourteen days after transection of the inferior alveolar nerve.[12] Furthermore electrical stimulation of the mandibular nerve resulted in the release of substance P from the tooth pulp.[13] Thus, substance P is not only present in dental pulp neurons but following neuronal excitation is released into the dental pulp.

The trigeminal neurons entering the brain stem (composed of medulla, pons and midbrain) terminate within one of the three trigeminal nuclei which are differentiated on the basis of the different cell types within each nucleus.

These three nuclei are distinguishable not only in cell type present there, but also in the type of sensory information received from the incoming trigeminal neurons. The mesencephalic nucleus receives proprioceptive information, the main sensory nucleus receives tough sensations and the spinal nucleus receives pain and temperature nerve fibers (figure 1). Substance P fibers entering the brain stem make a 90° turn to travel caudally before terminating in the spinal trigeminal nucleus. The fact that these are nerves originating from the dental pulp has been confirmed by histological studies showing cellular degeneration within the spinal trigeminal nucleus following extraction of a feline tooth.[14]

Thus substance P nerve fibers terminating within the brain stem mediate dental pain following activation within the tooth pulp. The fact that substance P is found in a specific group of sensory nerves suggests that different neurotransmitters are mediating other sensory functions such as touch, deep pressure and proprioception. Thus, future pharmacological research may develop drugs which specifically obtund the sensation of pain without altering the feelings of touch, deep pressure and proprioception.

A second function which substance P may mediate is the production of inflammation following release from nerves in the dental pulp. Production of hyperemia, edema and inflammation by nerves is itself a rather new concept. Inflammation has been studied by treating the skin with a powerful irritant such as mustard oil and then giving Evan blue dye intravenously. The blue dye is accumulated in the skin subjected to the irritant. If the nerves to this skin were cut and allowed to degenerate then no blue coloration would be observed following topical application of an irritant.[15] Similarly if the trigeminal nerve to the rat muzzle is stimulated, an increase in vascular permeability is observed.[16] These studies thus indicate, that nerves can and do regulate inflammatory responses even in the oral region.

To discern if substance P plays a role in this neurogenic induced edema, investigators have administered a compound which is called capsaicin.[17] Capsaicin administered repeatedly will release substance P from primary afferent neurons and acutely induce pain and inflammation.[18] However, following repeated administration of capsaicin, substance P will be depleted from primary afferent neurons and induce a state of analgesia.[19] The lack of pain is a selective effect on nociceptive neurons since the touch receptors for sneezing and corneal reflexes remain intact. When inflammation is studied in capsaicin-treated animals no blue dye is seen in the skin either following systemic administration[15] or direct application of capsaicin to the nerve innervating the skin. Thus it appears that substance P released from nerve terminals located within the dental pulp or gingival tissues functions as a vasodilator and to increase plasma extravasation. These local effects of substance P are not surprising because it is known to be a potent vasodilator and also to be anatomically closely related to blood vessels within these tissues.[12]

Substance P therefore appears to be mediating two functions which act to protect the tissues from injury. In other words, following mechanical or chemical insult to a tissue (e.g. tooth pulp) the substance P fibers are nonspecifically activated causing the release of substance P in both the tooth pulp and in the brain stem. In the tooth pulp the substance P functions to initiate inflammatory protective processes of vasodilation and increasing vascular permeability. In the brain stem the substance P sends pain messages to higher brain centers so that the appropriate central nervous system defense reactions may be elicited.

In summary, substance P has been found to mediate oral pain and inflammation. Both of these functions appear to be mediated simultaneously following mechanical or chemical activation of the primary afferent neurons containing substance P. Application of the knowledge of these processes involving substance P may provide useful approaches to better and more specific control of pain and inflammation in future dental clinical procedures.

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